1. Criticality of Particle Size Limitation

On page 4 of the Office Action, the Examiner states that Applicants' main argument was that none of the prior art references teach an organic acid salt in the form of powder or the specific mean diameter that improves skin permeability. In response, the Examiner states that "Applicants failed to show superior and unexpected results that show criticality in the claimed particle sizes." The Examiner further states that "It is within the skill in the art to determine the diameter of the particle in order to achieve a beneficial effect."

Applicants respectfully disagree because the specification does teach that there is a critical size of particles in the claimed invention to achieve the desired permeability. In particular, on page 4 of the specification Applicants stated (emphasis added):

> "During extensive researches to solve these problems the inventors found out that comprising an organic acid salt of a particular particle size in adhesive preparations containing a base drug as a salt form improves solubility of the drug to skin via an ion-pair formation, and that it significantly improves skin permeability of the drug by enhancing partition coefficient to skin, and thus accomplished the invention. Specifically, in case of the mean diameter of a base drug and an organic acid salt contained was 100μm or less (this particle size indicates volume average particle size when measured by the use of a particle fineness analyzer) the effect was observed. Particularly, it was revealed that in a fat-soluble base, though the solubility of a drug and an organic acid salt was so bad they remain as powder in the preparation, percutaneous absorbance of the drug was greatly affected by the size of the particle diameter of the organic acid salt. In particular, as an organic acid salt, the effect of sodium acetate is high, and in this case the average particle size of 0.1-10μm shows extremely excellent percutaneous drug-absorbance promoting effect.

Applicants also provided examples of the preparation of compositions with particle sizes of organic acid salt less than 100 μm. Comparative examples in which the particle sizes of organic acid salt were greater than 100 μm also were provided. When compositions of these two kinds were subjected to a skin permeability test on hairless mice, the results as shown in Figures 1-3 demonstrate that the compositions having particle size of less than 100 μm were superior, with a marked criticality corresponding to the size of the particles used in the compositions.

It is admittedly known that the smaller the size of a particle, the more quickly the particle can be dissolved in solution. However, the '946 patent merely describes a particle size of about 0.1 to 200 μm as pore forming solids, and all the examples disclosed in said patent relate to orally administered preparations, of which the active ingredients are absorbed through wet mucosa, but there are no examples of transdermal preparations.

The normal skin has a barrier function to prevent the penetration of foreign substances (see page 2, lines 7 to 8). Thus, the skin permeability of a transdermal preparation is not improvable only by making particle size smaller, but depends upon the "solubility of the drug to the skin" and the "partition coefficient to skin" as described on page 4, lines 12 and 14 to 15 in the present specification. Applicant first found that the skin permeability of the salt form of the base drug can be improved by means of the ion –pair formed by a particular particle size of the organic acid salt as described on page 4, lines 9 to 19.

2. Combination of References Not Sufficient

The Examiner also stated that the '946 patent is relied upon solely for its teaching of the use of a particular size of sodium acetate particles in pharmaceutical compositions. The Examiner then concludes that it would have been obvious for one of ordinary skill in the art to provide a pharmaceutical composition in powder form and to select a particle size of the powder that is required to achieve a desired rate of permeation.

The problem with this analysis is that the references relied upon for the rejection teach different types of pharmaceutical preparations, such that one of ordinary skill in the art would not combine the teachings of the primary references (the '374 and '157 patents) with the secondary reference (the '946 patent). In other words, the Examiner has not met the burden of showing that one of ordinary skill in the art would have a motivation to combine the references in the manner done by the Examiner. Even if the references were properly combined, the combination would not result in the claimed invention.

a. The combination of references doesn't teach the claimed invention

Specifically, while the '946 patent does teach the use of sodium acetate in pharmaceutical preparations, the particles are used for a completely different purpose than sodium acetate is used for in the '374 and '157 patents. In particular, the '946 patent describes the use of sodium acetate of the stated particle size in "pore forming solids," which are used as "pore forming agents suitable for the preparation of the microporous layer" in a coating of pressed disks, tablets and granulates. See column 6, lines 42-62 and column 5, lines 9-10.

The sodium acetate is not combined with other components in the manner of the claimed invention. It is important to note that the '946 patent relates to tablet and hard gelatin capsule (see all examples), in which the active ingredient of the tablet and hard gelatin capsule is absorbed through wet mucosa. Thus, a drug salt and an organic acid salt cannot form an ion-pair as in the claimed invention when the active ingredient is absorbed.

Applicants also note that the deficiencies of the '374 patent were explained in the "BACKGROUND ART" section of the patent application: "the aim of using these organic acids in the ['374 patent] is to improve stability and solubility, and was a pH-adjusting agent, and because these drugs are acidic or neutral, they are not the preparations in which skin permeability of a physiologically active substance is improved via an ion-pair formation constructed by an organic acid of the present invention." Thus the claims should not be rejected over the '374 reference.

Applicants further note that U.S. Patent 5,866,157 is owned by the present assignee, Hisamitsu Pharmaceutical Co., Inc., and corresponds to WO 96/16642 which is referred to as prior art in the "BACKGROUND ART" section of the patent application.

b. Proper motivation to combine is lacking

As is well established in the law, an effective obviousness rejection is based on references that provide a specific motivation for a skilled artisan to combine references in such a

way as to obtain the claimed invention. This was not achieved by the rejection issued by the Examiner.

The requirement for a specific motivation to combine the teachings of prior art references was recently set forth by the Court of Appeals for the Federal Circuit in In re Sang Su Lee. Applicants provide below an excerpt for the convenience of the Examiner.

> When patentability turns on the question of obviousness, the search for and analysis of the prior art includes evidence relevant to the finding of whether there is a teaching, motivation, or suggestion to select and combine the references relied on as evidence of obviousness. See, e.g., McGinley v. Franklin Sports, Inc., 262 F.3d 1339, 1351-52, 60 USPQ2d 1001, 1008 (Fed. Cir. 2001) ("the central question is whether there is reason to combine [the] references," a question of fact drawing on the Graham factors).
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> "The factual inquiry whether to combine references must be thorough and searching." Id. *It must be based on objective evidence of record.* This precedent has been reinforced in myriad decisions, and cannot be dispensed with. See, e.g., Brown & Williamson Tobacco Corp. v. Philip Morris Inc., 229 F.3d 1120, 1124-25, 56 USPQ2d 1456, 1459 (Fed. Cir. 2000) ("a showing of a suggestion, teaching, or motivation to combine the prior art references is an 'essential component of an obviousness holding'") (quoting C.R. Bard, Inc., v. M3 Systems, Inc., 157 F.3d 1340, 1352, 48 USPQ2d 1225, 1232 (Fed. Cir. 1998)); In re Dembiczak, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999) ("Our case law makes clear that the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references."); In re Dance, 160 F.3d 1339, 1343, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998) (there must be some motivation, suggestion, or teaching of the desirability of making the specific combination that was made by the applicant); In re Fine, 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988) ("'teachings of references can be combined only if there is some suggestion or incentive to do so.'") (emphasis in original) (quoting ACS Hosp. Sys., Inc. v. Montefiore Hosp., 732 F.2d 1572, 1577, 221 USPQ 929, 933 (Fed. Cir. 1984)).
>
> The need for specificity pervades this authority. See, e.g., In re Kotzab, 217 F.3d 1365, 1371, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000) ("particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed"); In re Rouffet, 149 F.3d 1350, 1359, 47 USPQ2d 1453, 1459 (Fed. Cir. 1998) ("even when the level of skill in the art is high, the Board must identify specifically the principle, known to one of ordinary skill, that suggests the claimed combination. In other words, the Board must explain the reasons one of ordinary skill in the art would have been motivated to select the references and to combine them to render the claimed invention obvious."); In re Fritch, 972 F.2d 1260, 1265, 23 USPQ2d 1780, 1783 (Fed. Cir. 1992) (the examiner can satisfy the burden of showing obviousness of the combination "only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references").

In re Sang Su Lee, slip op. 7-9 (Fed. Cir. 2002) (emphasis added except where noted).

The references do not provide the specific motivation to combine because, as noted above, the references contain differences in compositions used. In particular, the '374 and '157 patents do not teach any advantage in the use of organic acid in powder form, nor the use of particles of any particular size, and certainly do not teach the use of particles having a size less than 100 μm. The '946 patent teaches the use of an organic acid in powder form for use in coating of pressed disks, tablets and granulates, but does not teach the use of an organic acid in powder form for use in an adhesive preparation. Therefore none of the references provide the necessary motivation to combine the teachings in a way to obtain the invention now claimed by Applicants. The Examiner has not provided any other specific motivation under which one of ordinary skill in the art would combine the recited references. Accordingly, Applicants assert that the Examiner has not met this burden.

Despite the passage in the '374 patent: "As salt in the non-steroidal anti-inflammatory analgesic agent having a salt form which can be used in the present invention, any salts can be used so long as they are pharmaceutically acceptable. For example, alkali metal salts, alkaline earth metal salts, aluminum salts and the like are preferred" (see column 3, line 67 to column 4, line 4 in the '374 patent), all the drugs employed in the examples are acidic agents.

The transdermal base drug salt in the present invention not only enhances the partition coefficient to skin but also prevents the electrostatic interaction of the base drug salt with skin components negatively charged by carboxyl and phosphate groups on the cell surface (T. Ogiso et al., YAKUZAIGAKU ZASSI 120(4), 328-338 (2000); T. Ogiso et al., J. Pharm. Sci. 79(12), 1065 (1990); copies of these references are enclosed herewith for the Examiner's convenience). This absorbing mechanism of the base drug salt totally differs from that of the acidic drug salt.

Further, the '374 patent relates to converting non-steroidal anti-inflammatory analgesic agents into free-based drugs having higher oleophilicity (see column 4, lines 42-51 of said patent). The free-based drugs dose does not form the ion-pair whatsoever.

In summary, Applicants assert that the cited prior art patents, alone or in combination, do not teach or suggest the claimed invention. Moreover, Applicants did teach criticality of particle size in the claimed invention. Accordingly, Applicants respectfully request that the Examiner reconsider the rejection and withdraw the rejection of the claims under 35 U.S.C. 103.

CONCLUSION

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, which is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,

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